REMARKS

In accordance with the above amendments, claims 136, 139 and 144 have been canceled and claims 135, 140, 145-146 and 153 have been amended. New claims 156-159 have been added. Thus, claims 135, 137-138, 140-143 and 145-159 remain under consideration in the present application. It should be noted that the cancellation of claims has been done without prejudice or disclaimer of any of the subject matter therein. No claim stands allowed.

The specification has been amended on page 1 to update the priority information as requested in the Official Action. With respect to page 28, it appears that the text of the specification actually ends on page 27 and blank page 28 may be deleted.

New claims 156-159 are believed well-supported by the original contents of the specification. Claim 156 appears to be well-supported throughout the specification as numerous references are made to such a step. Claim 157 finds basis in both Example 6 and Example 10; claims 158 and 159 are, likewise, well-supported in Example 9.

As to the amendments to existing claims, they are also believed to be well supported in the materials originally submitted. Thus, in claim 135, one amendment involves including the feature that the polynucleotide is comprised in a virus or virus-derived DNA added to subparagraph (b) of claim 135. This

art would appreciate and be able to readily identify which fragments of the viral vectors were operative in facilitating the delivery of genetic material to male germ cells. We therefore believe that the written description is adequate.

Applicants believe that the claim rejection under 35 USC ∋ 112, second paragraph, has also been rendered moot by the cancellation of claim 139 and the amendment deleting the term "spermatogonia-specific" from claim 146. However, applicants are convinced, for example, that the other uptake enhancing DNA segments are ones which serve an equivalent purpose to the viral vectors; and it is believed that this would be recognized by one skilled in the art.

The rejection of claims 135, 136, 138, 139, 144, 147 and 150 under 35 USC ∋ 102(b) as being anticipated by Bachiller et al (1991) is respectfully traversed. There is no disclosure in Bachiller et al (1991) that the introduced DNA has been integrated into the genome of the sperm cell. In addition, Bachiller et al describes only the use of liposome/DNA as the transfecting agent which is not claimed in the present claims. Reconsideration and withdrawal of this rejection is respectfully requested.

The rejection of claims 135, 136, 138, 139, 144, 145, 147, 150, 151 and 152 under 35 USC ∋ 102(a) as being anticipated by Kim et al (1997) is also respectfully traversed. It is noted

that Kim et al (1997) also describes only the use of liposome/DNA complex as the transfecting agent. It is noted also that Kim et al explicitly states that their *in vitro* results showed that "liposome/DNA complexes can be bound into spermatozoa efficiently, but cannot be incorporated into their chromosome DNA" (see page 519, column 1 at lines 4-7). Thus applicants' claims are believed novel and not taught by Kim et al. Reconsideration and withdrawal of this rejection is respectfully requested.

Neither Bachiller et al (1991) nor Kim et al (1997) disclose, teach or suggest all the elements found in the present claims and so these references cannot be found to be anticipatory.

The rejection of claims 135-145 and 147-155 under 35 USC ∋ 102(e) as being anticipated by Brinster et al (U.S. 5,858,354) is also respectfully traversed. Although the Examiner is correct that Brinster et al do discuss that, in an optional embodiment of their invention, primitive cells may be modified genetically so that the genetic characteristics of the resulting spermatozoa can be predetermined (column 7, lines 37-40), there is no disclosure in Brinster that it is male germ cells that are modified genetically. While Brinster et al disclose a multitude of primitive cells including totipotent stem cells, embryonal carcinoma cells, embryonic stem cells, primordial germ cells,

other primitive cells etc (see column 5, line 64 to column 6, line 5), they do not specify which of these are to be genetically modified.

In fact, it is submitted that the teaching of Brinster et al would lead the skilled person away from the present inventive concept to modify other types of primitive cells. Firstly, note 5 referred to in column 7, line 38 is to the genetic modifications of teratocarcinoma and embryonic stem cells, and not male germ cells. Secondly, to emphasize this point, the reference to the Zfy-1 gene promoter in column 12 (referred to by the Examiner) is in the context of introducing a transgene into eggs to produce transgenic mice to provide eventual donor cells. Thus, the Brinster et al reference do not disclose the introduction of a polynucleotide encoding a desired trait into a male germ cell.

Furthermore, there is not suggestion in Brinster et al that only those cells in which the polynucleotide has incorporated into the genome of the germ cell should be selected.

For the above and other reasons, it is believed that the present claims clearly are novel and distinguish over Brinster et al.

Claims 135-137, 147 and 150 were rejected under 35 USC ∋ 103(a) as being unpatentable over Brinster et al (1994). The Examiner alleges that the claims are obvious over Brinster et al

(1994) on the basis that because it was known in the art that embryonic stem (ES) cells could genetically modified and that since Brinster et al allegedly suggests that spermatogonia could be cultured and manipulated as ES cells, then they could be used in a manner similar to ES cells for creating mice with germ line modifications.

Applicants believe that it is not proper to equate ES cells and spermatogonia since, biologically, they are very distinct and have very different properties. Because of these biological differences, there is no reason to suppose that spermatogonia would behave in a similar manner to ES cells and, in particular, there is no reason to suppose that spermatogonia could be transfected merely because it is suggested that ES cells have been in the past. Furthermore, even if spermatogonia could be transfected, there is not reason to suppose that they could be used to make transgenic animals in the way suggested by the Examiner.

We also refer the Examiner to Kim et al and Bachiller et al discussed above for additional reasons that follow.

The evidence of Kim et al is that using a standard transfection procedure, i.e., liposome/DNA complexes, spermatozoa cannot be tranfected so that the DNA is incorporated into their chromosome DNA (see page 519, column 1, lines 4-7).

The evidence of Bachiller et al is that when using a

standard transfection procedure, i.e., liposome/DNA complexes, to transfect sperm, the sperm does not generate transgenic animals (see last sentence of the Abstract).

Thus, the evidence of record is that there is no reasonable expectation of success in doing what the Examiner alleges is an obvious thing to do.

The present claims, on the other hand, are restricted to the polynucleotide to be transfected into the male germ cells being comprised in a virus or virus-derived DNA and germ cells being selected in which the polynucleotide has incorporated into the genome.

There is nothing in Brinster et al which suggests that virus (or viral-derived DNA) should be used for transfection of spermatogonia or that incorporation of the polynucleotide into the genome is necessary. Indeed, the failure of Kim et al and Bachiller et al to transfect spermatozoa and use the spermatozoa to generate transgenic animals would have dissuaded the skilled person from seriously contemplating what the Examiner is suggesting is obvious, particularly because the ES route of making transgenic animals was already available to him or her.

This, for the above and other reasons, the claims are not believed to be obvious over Brinster et al (1994).

The Examiner is requested to consider the amendments and remarks contained herein, and reconsider and withdraw the

rejections and allow the present claims. If issues remain that the Examiner believes can be resolved by telephone interview, he is invited to contact the undersigned attorney at his convenience to expedite prosecution of this application.

Respectfully submitted,

NIKOLAI & MERSEREAU, P.A.

C. G. Mersereau
Registration No. 26205
820 International Centre
900 Second Avenue So.
Minneapolis, MN 55402
(612) 339-7461